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BULLETIN
OF
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THE JOHNS HOPKINS PRESS

BALTIMORE, MARYLAND, U. S. A.

CHANGES IN TOTAL GASEOUS METABOLISM OF UNANESTHETIZED DOGS AFTER INTRAVENOUS INJECTION OF POSTERIOR PITUITARY EXTRACTS[1]

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Direct measurement of the total gaseous metabolism of unanesthetized dogs under the influence of post-pituitary extracts appeared a logical step in our investigations of the physiological rôle of the secretions elaborated in the posterior portion of the hypophysis. We had found (2) from blood studies on dogs that injections of pituitrin and pitressin (the pressor fraction of pituitrin) cause a definite chain of metabolic disturbances. The circulatory and respiratory effects may be summarized as follows: for a brief period (5 to 10 minutes) immediately following the intravenous administration of the drugs the blood draining the limbs is arterial in color and shows a high oxygen, a rapidly rising lactic acid and a concomitantly lowered carbon dioxide concentration; in addition, the blood sugar and inorganic phosphate are increased. This stage may be described as one approximating anaërobic metabolism in the tissues. The heart rate is slowed, the cardiac output is decreased (2), the skin capillaries are constricted, the blood pressure for the greater part is elevated, the veins are distended and the respiratory rate is very rapid. This period may be regarded as the stage of maximum activity of pituitrin and pitressin. In the recovery period immediately ensuing and lasting for a considerable time the picture is reversed: an increased oxygen consumption by the tissues, a further rise of lactic acid with subsequent lowering during the long recovery period, and a gradual return of carbon dioxide to a slightly subnormal level with some retention in the tissues. This period resembles in duration and blood picture the recovery period following brief severe muscular exercise.

However, the blood drawn from the external jugular vein, which in the dog has a mixed drainage area, namely brain, muscle, *etc.*, in the

[1] This work was aided by a grant from the Hartley Corporation.

period of the so-called "maximum action" of pituitrin and pitressin indicates a different effect of the drugs in this region. In contrast to the arterial-like character of the leg sample the external jugular blood is more venous in color, has a decreased oxygen content, and exhibits only a slight, if any, alteration in the carbon dioxide concentration, and a lactic acid increase similar to that in the femoral blood. The return to the basal level roughly parallels the recovery period as judged from the blood draining the limbs. The fact that there is such a striking difference in the venous blood of the limbs and that of the head regions was an added reason for determining the change that the total metabolism undergoes after pituitrin and pitressin.

The literature dealing with the metabolic effects of posterior pituitary extracts is reviewed in the recent publications of Himwich and Haynes (4) and of Grollman and Geiling (3), and hence need not be repeated here. Both groups of investigators point out the discordance in the results obtained by different workers, and ascribe the inconsistencies as being due to a variety of causes, such as dose, route of administration, animal species and time of metabolic measurements. Determinations of the oxygen consumption only once or twice after injection or over a long period of time following administration would result in a failure to recognize the different stages of the action of the drugs. For example, the measurement of the oxygen consumption in rats for hourly periods after the subcutaneous administration of large doses of chloretone-free pitressin in the experiments of Himwich and Haynes (4) did not bring out such a succession of changes as are obtained by the determination at frequent short intervals after a single intravenous injection of an average dose, as was previously made clear in our blood studies. However, the experiments herein reported, like the simultaneous determinations by Grollman and Geiling (3) on man, were performed under uniform conditions, and observations were made at frequent intervals during the course of action of the drugs. This method of experimentation enables one to detect the different stages of action and also furnishes the basis for reconciling the discordant results obtained by previous workers.

Most of the dogs used in our previous pituitary studies were employed in the present investigation. The animals were starved for 20 to 24 hours and were rested in a cool darkened room for an hour or more

preceding the experiment (according to the time required by each animal to reach a fairly low and constant pulse and respiratory rate). Each dog had its individual mask made of ordinary rubber inner tubing which was fitted around a circular metal rim of sufficient diameter to encircle the animal's mouth and nose comfortably. A short metal tube (2 inches long and $\frac{7}{8}$ inch in diameter) soldered to the center of this rim was fitted end-to-end with rubber tubing to a Douglas-Rosling valve, to the expiratory end of which was connected a three-way aluminum cock, arranged so that the mask valve system could be open to either the air or to the Douglas bag. After a preliminary washing out of the bags with the subject's expired air, two or three 10-minute normal collections were made. Because of the rapidly changing types of respiration elicited by the intravenous injection of pituitrin and pitressin the collection periods, after the administration of the drugs, had to be shortened so as to correspond with the different types of breathing. This was especially true of the period immediately following injection when the respiration is markedly slow and shallow for 5 to 6 minutes, after which rapid panting sets in suddenly and lasts for 10 to 20 minutes. The collection periods during the panting were gauged for each experiment and depended upon the intensity and duration of this type of respiration. In the prolonged recovery period the usual 10-minute samples were collected at frequent intervals for $1\frac{1}{2}$ to 2 hours until the volume of expired air per unit time had approached the pre-injection level. The cardiac and respiratory rates were counted at frequent intervals. In order to secure the coöperation of the animals during such long experimental periods when rest and quiet were so essential, a number of preliminary training experiments were necessary. It is interesting to note that several of the dogs definitely showed in each succeeding week the results of this training in the increasing consistency of two or three successive normal basal samples. Furthermore, the basal metabolic rates of the individual dogs, some of which were slightly above or below the accepted normal level, closely checked at different times, thus indicating the constant conditions under which the experiments were conducted. Although some control experiments carried out with the injection of saline (0.8 cc.) frequently demonstrated an evanescent increase in oxygen consumption in the period immediately following injection, this effect seldom lasted longer than the

first 10-minute period. Furthermore, such a transient rise would not vitiate the results obtained after pituitrin or pitressin, since these drugs consistently produce an immediate and marked fall in oxygen consumption which can thus be interpreted as the direct and specific effect of the drugs. However, we are inclined to interpret the results obtained with pitocin less positively, although the increased oxygen consumption frequently obtained with relatively large doses of this preparation is usually of a longer duration than could be attributed to any extraneous or secondary causes.

METHOD OF ANALYSIS

Oxygen and carbon dioxide determinations were made in a Haldane apparatus. The oxygen consumption is expressed in cubic centimeters per minute per square meter of body surface, as calculated by Meeh's formula for the dog.

RESULTS

Chart 1, which is typical of the results obtained by the injection of pitressin, gives a composite picture of the changes in oxygen and carbon dioxide, lactic acid, pulse rate, and oxygen consumption, as determined in three separate experiments on the same dog. Although the blood and metabolic studies were separated in time by approximately ten months, there is an almost exact correspondence between the period of decreased oxygen consumption as determined from the analysis of expired air, and the "arterial" oxygen and lowered carbon dioxide and rising lactic acid content of the venous (leg) blood. In the second prolonged period, in which the oxygen consumption is increased above the normal level, the venous blood has an abnormally low oxygen concentration, indicating an increased utilization of oxygen by the tissues. The recovery curves are similar in gradation and time. Despite the fact that the oxygen consumption reached its initial level the respiratory quotient sometimes remained low. Although we are not prepared to offer a definite explanation several possibilities may be considered:

1. Incomplete recovery with the lactic acid above the initial level, and continued retention of carbon dioxide.
2. Fat metabolism, which would give a low R. Q.

3. Conversion of fat into carbohydrate, which would give a very low quotient, and, with a simultaneous oxidation of the carbohydrate which is formed from the fat, would yield a resultant quotient corresponding to those obtained in some of our experiments.

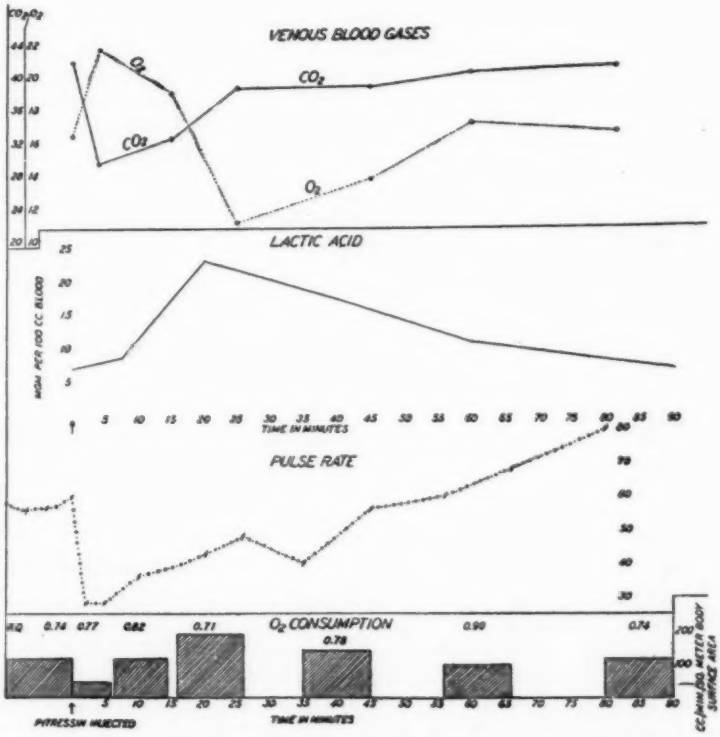

CHART 1. THE EFFECT OF INTRAVENOUS INJECTIONS OF PITRESSIN [0.4–0.5 CC.] ON THE VENOUS BLOOD GASES, LACTIC ACID, PULSE RATE, AND O_2 CONSUMPTION

The two last named possibilities are made with reservations because of the difficulty of determining and evaluating the significance of the R. Q. in animals.

The results obtained with pituitrin are essentially similar to those secured with pitressin, as will be seen in Chart 2, which was chosen

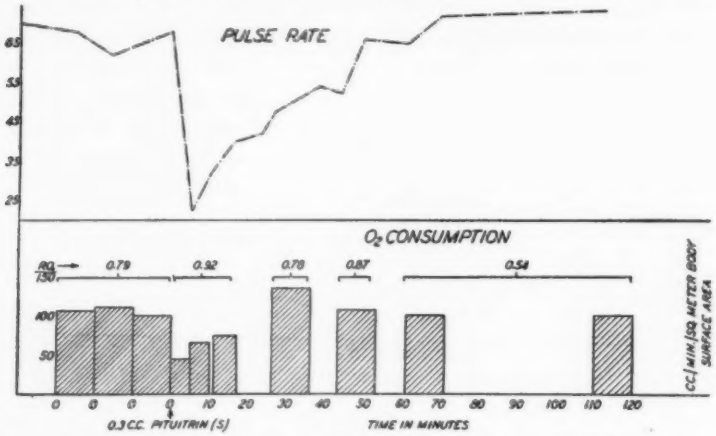

CHART 2. THE EFFECT OF INTRAVENOUS INJECTION OF PITUITRIN [S](0.3 CC.) ON THE PULSE RATE AND O_2 CONSUMPTION

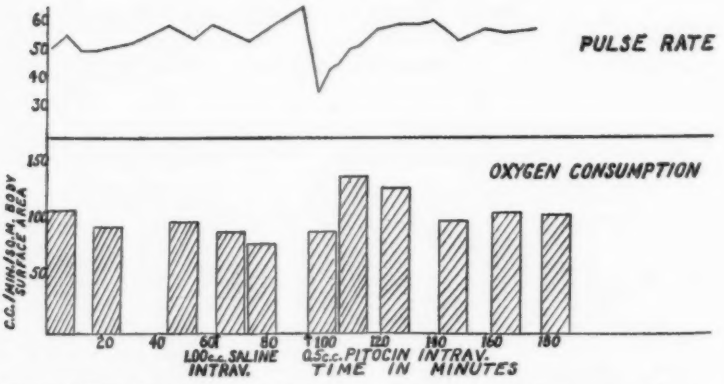

CHART 3. THE EFFECT OF THE INTRAVENOUS INJECTION OF SALINE AND PITOCIN (CONTAINING 0.1 PER CENT PITRESSIN) ON THE PULSE RATE AND O_2 CONSUMPTION OF A NORMAL UNANESTHETIZED DOG

to illustrate the fact of the low R. Q. referred to above. It should be pointed out that the recovery period is unusually long in the dog used for this experiment.

TABLE 1

Changes in oxygen consumption of normal, unanesthetized dogs following the intravenous injection of pitressin and pituitrin (S)

TIME WHEN COLLECTION STARTED	DURATION OF COLLECTION	OXYGEN CONSUMPTION	R.Q.	PULSE RATE	RESPIRATION	REMARKS
Dog—15.3 kg.—Dose = 0.4 cc. pitressin (8 international units)						
	minutes	*cc./min./sq. m. body surface*		*per minute*	*per minute*	
9:36 a.m.	10	93.45	0.76	51	18	
9:55	10	89.88	0.79	60	23	
10:38—injected intravenously 0.4 cc. pitressin						
10:38	5′15″	22.73	1.00	52		Pulse weak, panting
10:43½	6	93.62	0.83	62		
10:53	7	136.2	0.89			Mask removed because of panting
11:43	10	87.32	0.92	70		No panting
12:03 p.m.	10	102.1	0.82	68		
12:24	10	100.7	0.69	64		
Dog—20 kg.—Dose = 0.25 cc. (5 international units) pitressin						
10:57 a.m.	10	108.3	0.73	50	11	
11:32½—injected intravenously 0.25 cc. pitressin						
11:32½	6	63.01	0.83	31	15	
11:39	10	73.26	0.81	36	13	
11:49	10	133.9	0.75	46		
12:01 p.m.	10	130.0	0.77	46		
12:27	10	79.42	0.77	52		
12:41	10	114.1	0.76	54		
Dog—15 kg.—Dose = 0.3 cc. surgical pituitrin (7 international units)						
10:32 a.m.	10	86.24	0.84	62	15	
10:43	10	75.53	0.92	60		
11:01	10	78.89	0.85	64	14	
11:24—injected intravenously 0.3 cc. pituitrin (S)						
11:24	4′45″	35.54	0.78			Started to pant at end of this period of collection
11:30	5	95.70	0.99	35		Panting. Vomited at 11:35 a.m. Stopped collection at once and removed mask
11:36	8′45″	124.7	1.12	42		
11:56	10	96.63	0.87	52	18	
12:31 p.m.	10	109.6	0.81	60	15	

In Table 1 are given some additional figures of experiments with varying doses of pitressin and pituitrin on dogs other than those used for charts 1 and 2. That very small doses of the drugs will produce these changes is shown by one of our experiments (not included in the table) in which the injection of $\frac{1}{20}$ cc. of pitressin caused a decrease in metabolism of over 50 per cent for 5 to 10 minutes after injection; thereafter the metabolism rose above the initial level and later returned to the resting value.

It is known that the admixture of even a small amount of pitressin complicates and may even mask the physiological effects of pitocin. Hence it is necessary in experimental work to use preparations of pitocin as free as possible of the pressor fraction. Dr. Kamm of Parke, Davis and Company kindly supplied us, for use in this investigation, with a specially pure lot of pitocin which contained only 0.1 per cent pitressin. In the doses employed this pitocin (0.5 to 1.0 cc. intravenously) invariably causes a decided drop in the pulse rate. Whether this is an intrinsic property of the substance or due to the very small amount of pitressin present cannot now be decided. In regard to its effect on the oxygen consumption the action of pitocin is not nearly so well defined as in the case of pitressin or pituitrin (S), although in some of our experiments the purified oxytocic fraction did produce a definite increase in oxygen consumption of longer duration than was usually observed when saline control injections were made. Chart 3 is illustrative of the statements made above. It is necessary to emphasize that in some experiments no appreciable change in the metabolism was observed with 0.5 cc. doses; then again, injections of 1 cc. elicited an increase in metabolism, but this was not sufficiently pronounced to warrant any definite conclusions. Attention should also be called to the fact that for a few minutes (4 to 5) immediately after the intravenous injection of a potent preparation of pitocin an increased liberation of heat through the skin is quite perceptible on palpation.

DISCUSSION

It is apparent from the data presented that post-pituitary extracts markedly affect the total body metabolism. The intravenous injection of pituitrin or pitressin in doses ranging from 0.2 to 0.6 cc. immediately produces a precipitous decrease in the oxygen consump-

tion for a brief period, which is followed by a prompt increase to a value considerably above the pre-injection level and finally by a gradual return to normal. These changes, in a milder degree, have been observed with doses as small as $\frac{1}{20}$ cc. of pitressin. Our data thus furnish the basis for harmonizing the discordant results reported by previous workers in this field. For instance, a determination made shortly after intravenous injection will show a decrease in metabolism. On the other hand, if the measurement is made 15 to 25 minutes after injection, during the compensatory stage, an increase in metabolism will be noted. Again, if the metabolism is measured over the whole period of action of the drug without differentiating between the different stages, the net effect may be either a decrease or an increase, depending on whether the stage of decreased metabolism exceeded the later period of increased oxygen consumption or vice versa.

With subcutaneous injection the slow absorption may prolong both the period of action (decreased metabolism) and the recovery period (increased metabolism), and may even cause the two stages to overlap, thus rendering a separation into distinct phases of action difficult.

These theoretical possibilities fit in with the results obtained on rats by Himwich and Haynes (4). During the first hour after subcutaneous injection of a small dose of pitressin they found a slight increase or very little change in the oxygen consumption; after a large dose, a marked decrease lasting several hours was obtained. Of course, in all such work there is considerable variation in the intensity and duration of the different stages of the action, depending on the dosage, route of administration and the animal.

The rôle of the oxytocic fraction in body metabolism, as judged from the results of injections of potent extracts, cannot be so clearly defined as in the case of pitressin. Nevertheless, in appropriate doses purified pitocin caused a definite increase in oxygen consumption in the majority of our tests. While pitressin and pitocin have, in a sense, opposite actions, one can conceive that they function in an harmonious way as one of the controlling mechanisms in the metabolism of the body. The contrast in their effects is an added factor which may help to explain some of the earlier discordant results obtained with pituitrin.

The mechanism through which the posterior pituitary extracts

bring about the metabolic changes within the body is not as yet clear. In addition to various possible factors—vascular or cellular—which were discussed in a previous communication (see also Himwich and Haynes), one must take into account the possible action of these drugs upon a central thermo-regulating mechanism (1). Moreover, it needs to be remembered that the drugs used in this study were by no means pure and only when they shall have been prepared as chemical individuals can conclusive experiments be made. In the meantime the results obtained with these impure preparations warrant only a tentative acceptance.

Owing to the inadequacy of our knowledge of the chemistry of the posterior lobe secretions and the lack of a specific test, either biological or chemical, for the hormones, we do not know as yet whether they are continuously escaping from the gland into the blood stream, or whether they are only given off on demand. The fact that one can obtain from the blood substances which have a pressor and oxytocic action is not sufficiently specific evidence of the presence of the posterior lobe secretion in the circulation. Since we lack this knowledge, we cannot devise methods for experimentally introducing the gland product from without in such a way as to simulate its physiological liberation from the gland and its subsequent rôle in the body. Hence, we must be content, for the present at least, with attempts to interpret results obtained on a markedly exaggerated scale. No doubt, even the most refined experiments of the kind here reported are gross exaggerations of the normal rôle which the hormones play in the orderly regulation of body functions, for one does not observe reactions normally in animals or in human beings such as are elicited by introducing at one time even very small amounts of extracts. If one accepts the postulate that the posterior lobe secretion functions as one of the important regulators of metabolism, then one must conceive of it as acting in very minute concentrations which do not bring about precipitous changes such as follow injections of potent extracts.

SUMMARY

Direct measurement of the total gaseous metabolism of unanesthetized dogs after intravenous injections of pituitrin, pitressin and pitocin shows:

1. A marked decrease in oxygen consumption during the period of maximum action of pituitrin and pitressin, followed by a more prolonged period of increased oxygen consumption above the initial level, then a gradual return to normal. These changes parallel the alterations in blood gases as described by us (2).

2. The results with pitocin, though not constant, show an increase in oxygen consumption in the majority of tests.

3. Our studies on dogs parallel the findings on man with therapeutic doses of the posterior pituitary preparations as reported by Grollman and Geiling (3).

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ON THE ETIOLOGY AND PATHOGENESIS OF WHOOPING-COUGH

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The literature concerned with the etiology of whooping-cough is far from satisfactory from the standpoint of clearly establishing the Bordet-Gengou bacillus as the specific causative agent of the disease. It is true that many investigators have reported the presence of this bacillus in a very high percentage of cases early in the disease, but others, with presumably as good technique, have been less successful in demonstrating its constant presence, and it is quite generally agreed that the bacillus can only rarely be found after the early stages, in spite of the fact that the symptoms continue in full force. Furthermore, it is fair to say that whooping-cough has never been reproduced experimentally in a truly satisfying manner by means of the Bordet-Gengou bacillus. In the hands of most investigators nothing really comparable to whooping-cough has been produced by placing pure cultures of this bacillus in the respiratory tract, and many different workers have used a wide variety of experimental animals in the attempt. Indeed, in the experiments of the majority of investigators the bacillus has produced no symptoms at all.

Mallory, who discovered the localization of the Bordet-Gengou bacillus in the cilia of the respiratory tract, and who regarded their etiological rôle as proven, carried out experiments in collaboration with Horner and Henderson (1) in which pure cultures of the bacillus were introduced directly into the trachea in three monkeys. No symptoms of any sort appeared. Four rabbits were then repeatedly inoculated intranasally and "no coughing or sneezing was ever observed." Six puppies were inoculated intratracheally with pure cultures. Four of the inoculations were described as "negative;" no symptoms are mentioned as occurring in the two other puppies but sections of the trachea showed some Gram-negative bacilli in the cilia. Subsequent workers (2) (3) have objected that those bacilli were probably *B.*

bronchisepticus, which is commonly found in the cilia of the trachea in the dog; and Mallory himself later reported experiments which substantiated that objection (27). All in all, these experiments must be regarded as completely negative as far as the experimental production of the disease "whooping-cough" is concerned.

Wollstein (4) sprayed pure cultures of the Bordet-Gengou bacillus into the mouth and nose of monkeys, cats and dogs. Two of the dogs developed distemper (no Bordet-Gengou bacilli recoverable at autopsy); the other animals showed no symptoms. The bacilli were then injected directly into the trachea of monkeys, but no symptoms followed.

Numerous other investigators have been similarly unsuccessful in their attempts to produce the disease with the Bordet-Gengou bacillus, among whom may be mentioned Arnheim (5), Bachmann and Burghard (6), Melfi (9) and Polett (10).

Sauer and Hambrecht (11) have recently reported the production of a cough in monkeys by means of the Bordet-Gengou bacillus. However, it was in only eight out of seventy-six attempts that a cough was produced, and in each of these eight instances large amounts of a pure culture (one to three cubic centimeters) had to be forced directly into the trachea in order to induce a cough. One may be permitted to suspect that any one of a number of pathogenic bacteria might provoke tracheitis, bronchitis and coughing if introduced intratracheally in such quantities. Indeed, Cecil and Blake (12), when studying influenza-bacillus infection of the respiratory tract, produced "a frequent, severe racking cough" in monkeys with pure cultures of the influenza bacillus. Furthermore, two of Sauer and Hambrecht's monkeys killed during the period of the cough were found to be suffering from pneumonia, and in a third monkey killed at the height of the cough the Bordet-Gengou bacillus could not be recovered from the trachea, and cough plates had been negative during life. In four of the eight coughing animals the lymphocytes rose well above their original levels, but in none of those four cases did the number of lymphocytes surpass the level recorded by Sauer and Hambrecht as normal for other monkeys in their series. In view of these considerations, and of the numerous unsuccessful attempts on the part of others even when the same animal and the same method of infection was used, it is difficult to regard the experiments of Sauer and Hambrecht, and

of the several others who have reported the experimental production of a cough (8) (28) (29), as having established the etiological rôle of the Bordet-Gengou bacillus in pertussis. At the least it may be said that the fulfillment of Koch's postulates can hardly be regarded as having been satisfactorily accomplished in the case of pertussis and the Bordet-Gengou bacillus.

Even though the presence of the Bordet-Gengou bacillus be admitted in a high percentage of cases of pertussis in the beginning of the disease, it rarely can be cultivated after the early days of the cough, and yet the cough continues in intensity for a period of weeks after the bacillus has disappeared from the tracheal exudate. Ordinarily during this time, however, and indeed in many cases from the very beginning, the influenza bacillus can easily be found. At autopsy in fatal cases it is very common to be able to isolate the influenza bacillus, often in pure culture, from the trachea and bronchi. There have been cases in this Department in which death occurred in clinically typical pertussis (lymphocytosis) uncomplicated by pneumonia, and in which the influenza bacillus, and not the Bordet-Gengou bacillus, was isolated from the lung.[1] These cases show microscopically the mononuclear-cell infiltration of the bronchial walls which we shall discuss below as a characteristic of pertussis, and bacterial stains show the presence of myriads of minute, Gram-negative bacilli entangled in the cilia of the bronchi, in spite of the fact that no Bordet-Gengou bacilli were recovered from the lung. I have been unable to find in the literature any demonstration that influenza bacilli localize in the cilia, but such cases as I have mentioned made it seem probable that this closely related bacillus might possess the same tendency to inhabit the ciliated margin of the epithelial cells as does the Bordet-Gengou bacillus. However, since there could always be some doubt as to the real nature of the bacilli found in the cilia in these cases of whooping-cough, even though the Bordet-Gengou bacillus was not cultivated and the influenza bacillus was, it seemed worthwhile to examine in the same manner material from fatal cases of influenza and of measles compli-

[1] By "influenza bacilli" are meant Gram-negative, haemophilic bacilli which ferment dextrose, form indol and reduce nitrates. Those which neither ferment sugar, form indol, nor reduce nitrates are classed as Bordet-Gengou bacilli. The latter also, of course, require a special medium for their isolation.

cated by influenza bacillus pneumonia, for in such cases if Gram-negative bacilli were found in the cilia no question of the added presence of the Bordet-Gengou bacillus with failure to cultivate it could be reasonably entertained. I have therefore studied cases of epidemic influenza and of measles, in which death occurred from interstitial pneumonia and in which the influenza bacillus was cultivated from the lung. *In the cases in which the cilia were well preserved the bacterial stains of the lung show that the influenza bacilli are entangled in the cilia of the air passages in a manner precisely like that in which the Bordet-Gengou bacillus localizes in that site in whooping-cough* (Figs. 2 and 3). It would be impossible to differentiate microscopically between influenza bacilli entangled in the cilia in a case of measles with influenza-bacillus infection of the respiratory tract, and Bordet-Gengou bacilli entangled in the cilia in whooping-cough. It is perfectly clear that the influenza bacillus possesses the same curious tendency to localize in the cilia as does the closely related Bordet-Gengou bacillus. One can no longer conclude, therefore, from the presence of minute, Gram-negative bacilli entangled in the cilia in autopsies on cases of whooping-cough that the bacilli under observation are necessarily Bordet-Gengou bacilli. They may very well be influenza bacilli and, indeed, undoubtedly are so in many cases, for death from pneumonia ordinarily occurs late in the disease at a time when Bordet-Gengou bacilli are rarely found in the tracheal exudate but when influenza bacilli are found with very great frequency; and influenza-bacillus pneumonia is well known to be common in fatal cases of pertussis.

Since the influenza bacillus localizes in the cilia exactly as does the Bordet-Gengou bacillus, and since it is generally believed that the presence of the latter in the cilia provides the irritation responsible for the cough in pertussis, it is a matter of some interest to note that a pertussis-like cough is not uncommon in epidemic influenza with influenza-bacillus infection of the respiratory tract (15) (16). Indeed, the very word for whooping-cough which is used by the French—*coqueluche*—is said to have been applied to the attacks of coughing in epidemic influenza before it was used to designate the cough of pertussis (14). It is of further interest that, in the discussion of the symptoms of influenza-bacillus infection of the respiratory tract, a standard textbook of Pediatrics (Holt and Howland (17)) states that there may

be "a paroxysmal cough which is hard to distinguish from pertussis. Such a cough we have seen continue for from four to six weeks with paroxysms so severe as to excite vomiting. We have observed it in families of children who had previously had pertussis. Bordet's bacillus could not be discovered in the sputum but the influenza bacillus was present. There was no lymphocytosis. It is not unlikely that many of the reported instances of second attacks of pertussis are of this nature." Holt (18), further, in an article on cases of bronchitis caused by the influenza bacillus states that that condition "may be characterized by a paroxysmal cough which is so like the paroxysms of pertussis that at times the two are indistinguishable." I have referred above to the "frequent, severe racking cough" observed by Cecil and Blake in their monkeys infected experimentally with influenza bacilli. These clinical, experimental and morphological observations indicate that not only the Bordet-Gengou bacillus but also the very closely related influenza bacillus is able to produce a paroxysmal cough by reason of its similar tendency to localize in the cilia of the trachea and bronchi. *B. bronchisepticus* occurring in dog distemper is another minute, Gram-negative organism which shares this peculiar predilection for localizing in the cilia. It is therefore interesting to note that when the respiratory tract of human beings has been infected by this organism a "pertussis-like cough" has been a prominent symptom (2).

When whooping-cough terminates fatally with pneumonia, as it does all too frequently, the pathological changes in the lung have long been recognized to be of the peculiar type designated as "interstitial bronchopneumonia." The chief distinguishing characteristic of interstitial pneumonia as contrasted with ordinary lobular pneumonia is the presence of an infiltration of mononuclear wandering cells (lymphocytes, plasma cells, macrophages) within the walls of the bronchi and bronchioles. Sometimes the alveolar septa extending from the affected bronchioles are also markedly thickened by the same type of inflammatory-cell infiltration. In some cases, in the pneumonic exudate free in the alveoli there may be a greater proportion of mononuclear cells than one encounters in ordinary lobular pneumonia, but in most cases the exudate in the alveoli and in the bronchial lumina is predominantly polymorphonuclear, and is quite indistinguishable

from that seen in any acute, pyogenic pneumonia. Interstitial pneumonia, therefore, differs from ordinary lobular pneumonia chiefly in the curious fact that the bronchial walls are thickened by an infiltration of *mononuclear cells*, whereas in lobular pneumonia they are either normal, or else contain a slight scattering of polymorphonuclear cells.

Several years ago there came to autopsy in this Department a case of pertussis in which death had occurred during convulsions, in the complete absence of pneumonia. Other similar cases have since been observed. It was striking that in these cases the bronchial walls showed exactly the same thickening and infiltration with mononuclear cells as is seen in interstitial pneumonia (Fig. 1). The question naturally arose, therefore, whether the curious mononuclear infiltration seen in interstitial pneumonia following pertussis might not be a lesion produced by pertussis itself, rather than by the bacteria responsible for the terminal pneumonia, as is ordinarily stated; for had an ordinary lobular pneumonia been superimposed upon the bronchial infiltration present in these lungs, a diagnosis of interstitial pneumonia would certainly have been made. On studying the literature it was found that several writers have regarded the mononuclear-cell infiltration of the bronchial walls as a specific effect of the Bordet-Gengou bacilli localized in the cilia. However, in view of the facts that the influenza bacillus is so commonly present in the disease, that it, too, localizes in the cilia, and that it is so frequently responsible for the terminal pneumonia, it, too, must be included among the possible causes of the interstitial infiltration. As a matter of fact, the influenza bacillus is very widely regarded as one of the chief causes of interstitial pneumonia wherever it occurs. Somewhat against this view is the fact that the influenza bacillus is a pyogenic microörganism which attracts polymorphonuclear, not mononuclear cells. The exudate in influenzal meningitis, for example, is a purulent one; and, indeed, at the sites where influenza bacilli are found in interstitial pneumonia—in the lumina of the bronchi and in the alveoli—the exudate is ordinarily polymorphonuclear. It seems strange, therefore, that this pyogenic organism should provoke a polymorphonuclear reaction everywhere except in the bronchial walls, and that in that one situation it should call out masses of mononuclear cells instead. As a matter of fact, although present in abundance in the polymorphonuclear exudate

in the alveoli and bronchi, it is exceedingly rare to find an influenza bacillus in the bronchial wall where the mononuclear-cell infiltration lies. If we turn to experimental work for an answer, we find that when the influenza bacillus has been introduced into the trachea of animals the resulting pneumonia has not been an interstitial one with mononuclear-cell infiltration of the bronchial walls. In the experiments of Cecil and Blake (12) on monkeys, and in those of Wollstein and Meltzer (20) on dogs, the intratracheal introduction of influenza bacilli caused only a *purulent* bronchitis and bronchiolitis, with or without frank pneumonia, but the mononuclear-cell infiltration of the bronchial walls characteristic of interstitial pneumonia did not appear.

If there are reasons for hesitating to believe that the pyogenic influenza bacillus is responsible for the mononuclear-cell infiltration of the bronchial wall, the same objections apply to the other bacteria which are associated with interstitial pneumonia, for all of them—streptococci, pneumococci, the Bordet-Gengou bacillus—are pyogenic bacteria, and none of them tend to invade the bronchial wall where the mononuclear-cell infiltration is located. If these bacteria are responsible for the interstitial reaction, as they are said to be, they must cause it by the elaboration of a diffusible toxic material, and at present we know nothing of the existence of toxic products of these microörganisms which specifically attract mononuclear cells. Furthermore, the interstitial process cannot be regarded as merely a subacute inflammation, which is characterized by the presence of many mononuclear cells; for the mononuclear-cell infiltration occurs in interstitial pneumonia associated with epidemic influenza when the entire duration of the disease has been only several days, and it does not occur in ordinary lobular pneumonia of the same or longer duration—unless the process becomes very chronic indeed.

Now it is important that interstitial pneumonia occurs not only in whooping-cough, but also as a complication of influenza and measles—indeed, almost exclusively in association with these three diseases. That it may rarely be found in cases in which none of these three predisposing diseases have been proved to have been present need not be questioned. It remains true that the vast majority of cases of interstitial pneumonia encountered in any autopsy service occur in association with whooping-cough, measles and influenza. Since the

latter two diseases are, in high probability, caused by filterable viruses, and since both are distinctly diseases of the respiratory tract, the suspicion naturally arises that the mononuclear-cell infiltration of the bronchial walls may represent a characteristic effect of certain virus diseases of the respiratory tract,[2] and that a filterable virus may be associated with pertussis itself.

There are indeed a number of considerations which point to the possibility that an invisible virus may play a rôle in the etiology of pertussis. Prominent among them may be mentioned the extreme infectivity of the disease, the durable immunity conferred by an attack, and the not infrequent complication of a specific encephalitis. In these three particulars, and in other important clinical and pathological ones besides, pertussis resembles in an extraordinary manner the distemper of dogs. There, too, the infectivity is great, the immunity is durable, and encephalitis is common. In distemper, too, a small Gram-negative bacillus (*B. bronchisepticus*) is constantly found; and interestingly enough, as has been said, this bacillus exhibits the same curious tendency to localize in the cilia of the respiratory tract of the dog as does the Bordet-Gengou bacillus in the human being. For a long while, therefore, *B. bronchisepticus* was regarded as the cause of dog distemper, and certainly on bacteriological, morphological and experimental grounds as good as those on which the Bordet-Gengou bacillus rests as the cause of pertussis. In 1926, however, it was shown by Dunkin and Laidlaw (21) that distemper is really caused by a filterable virus, and that *B. bronchisepticus* is merely a concomitant invader comparable, in a way, to the bacillus of hog cholera which so regularly accompanies the true, filterable, etiological agent of that disease, and which was long regarded as the sole cause of hog cholera. The very close analogy between whooping-cough and distemper strongly suggests that the primary cause of pertussis may be a filterable virus, and that the Bordet-Gengou bacillus and the influenza bacillus may be only concomitant invaders which, as in the case of *B. bronchisepticus*, by reason of their tendency to localize in the cilia of the trachea and

[2] It is of interest that the interstitial infiltration was beautifully shown in each of two cases of psittacosis which I have had an opportunity to study. Psittacosis is, of course, now known to be caused by a filterable virus (Bedson, Western and Simpson, **Lancet,** 1930, I, 235).

bronchi, provoke coughing by the irritative effect of their presence in this sensitive site.

In favor of the view that an invisible virus may be responsible for the mononuclear-cell infiltration of the bronchial walls which is found in the interstitial pneumonia complicating influenza, measles and pertussis, there is the fact that even pure pneumococcal pneumonia occurring during the influenza epidemic has assumed the character of interstitial pneumonia. MacCallum (22) describes such cases in his monograph on influenzal pneumonia, and the microscopical sections of those cases in which the pneumococcus was the only organism cultivated from the lung, and the only one discoverable in bacterial stains adapted to reveal effectively Gram-negative as well as Gram-positive bacteria, show a brilliant interstitial pneumonia. I have carefully examined the sections from forty cases of pneumococcal pneumonia not associated with influenza, measles or whooping-cough, and in not a single case have I encountered the interstitial mononuclear-cell infiltration. This tends at least to indicate that the bronchial infiltration in the influenzal cases may have been the result not of the pneumococcus, but rather of an underlying virus; and the same possibility applies to the interstitial infiltration in whooping-cough.

A search of the literature shows that it has occurred to several observers that the interstitial infiltration in whooping-cough may be the effect of an invisible virus. Thus, Lauche (23) writes: "Mann kann auch daran denken, dass die Ähnlichkeit dieser Pneumonieformen damit zuzammenhängt, dass sowohl das Virus der Masern, wie des Keuchhustens, wie schliesslich der Grippe—als filtrierbare mikroorganismen (?)—alle eine gleichartige Reaktion des Körpers in der Lunge hervorrufen." And, in the same vein, Jochmann and Hegler in their textbook (24) write; "Es erscheint durchaus naheliegend—ähnlich wie für die Aetiologie der Grippe—anzunehmen, dass der Erreger des Keuchhustens ein noch unbekenntes Virus ist, zu welchem als Mischinfektion in der ersten Krankheitsperiod hauptsächlich der Bordet-Gengousche, später der Influenzabacillus, sich hinzugesellt."

In a disease in which a filterable virus is suspected as the etiological agent, the search for inclusion bodies is an obvious procedure. For a number of years, therefore, I have kept a lookout for inclusion

bodies in the lungs and trachea of children dying of pertussis. In five cases (autopsies nos. 8586, 8644, 8805, 8820 and 9122) intranuclear inclusions have been present in striking degree. Perhaps they were present less conspicuously in other cases, for I have not minutely examined every cell in every section of the lungs in each case, although I have done so in a number of cases without success. In these five cases the greatly enlarged alveolar and bronchial epithelial cells contain huge nuclei, in which lie large round or oval inclusions (Figs. 5, 6, 7); some of the enlarged cells show cytoplasmic inclusions as well or, at least, small, round fuchsin-staining bodies. Inclusion bodies occurring in the lung in pertussis have previously been reported. Several years ago Feyrter (25) described and pictured enlarged alveolar cells with intranuclear inclusions in pertussis, which are in all respects identical with the cells in our cases. He attributed them to the probable presence of a specific virus. It should be stated, however, that these cells are also identical with those described by Von Glahn and Pappenheimer (19) in the lung of an adult in whom there was no question of pertussis, and by Goodpasture and Teague (26) as a result of introducing the virus of herpes into the trachea of animals. In one of our five cases in which inclusion bodies were found, the presence of herpes labialis was noted at autopsy. Whether this condition was present but overlooked in the other four cases I do not know, but herpes is well known to be very common during pneumonia in children. In the clinical histories of two of the other cases there is a diagnosis of "apthous stomatitis" which also is a very common condition in children. The etiology of ordinary apthous stomatitis is unknown, but it may resemble herpetic stomatitis so closely that a differential diagnosis becomes difficult (13). Indeed, some writers regard every case of "apthous stomatitis" as herpetic (7). In spite of the fact that there are reasons for searching for the presence of inclusion bodies in the lung due to a specific virus of pertussis, the possibility of the aspiration of herpes virus in these cases can by no means be entirely neglected. The inclusion bodies may possibly be related to pertussis itself, but they may also be the result of the aspiration of herpes virus, or of the presence of some other obscure virus disease, such as that described by Von Glahn and Pappenheimer. For the present the question must be left open. Experiments are being carried out in the attempt to answer it.

Now it is important to record that in two of these cases of frank pertussis (autopsies 9122 and 8644) in which inclusion bodies were present in great abundance in sections made through different parts of the lung, there was no appreciable mononuclear-cell infiltration of the bronchial walls (Fig. 4), although this infiltration is almost invariably present in pertussis. In a third case (autopsy no. 8820) the bronchial walls were densely infiltrated with polymorphonuclear leucocytes, but there were only occasional mononuclear cells in the exudate. Death occurred in each of these three cases late in the disease—in each instance more than four weeks after the onset of pertussis—so it cannot be assumed that these represent early stages of the disease which would have given way later to the mononuclear-cell infiltration. In autopsy no. 8820, *Streptococcus pyogenes* and *Pneumococcus II* were isolated from the lung, and in addition a minute Gram-negative organism (Bordet-Gengou bacillus (?) influenza bacillus (?)) was stained in the sections. In autopsy no. 8644, *Streptococcus pyogenes* was cultivated and, again, a minute, Gram-negative organism stained in sections. This latter organism was undoubtedly overgrown by the streptococci in both cases. No cultures were made in autopsy no. 9122, but bacterial stains of the lung show many minute, Gram-negative bacilli entangled in the cilia.

These three cases must at least place us on our guard against any premature conclusion that the interstitial infiltration of the lung in pertussis is the result of an unseen virus, in spite of the reasons which tend to make one suspect that it is. Certainly, if the intranuclear inclusions in these cases are the result of a filterable virus of pertussis, it is clear that the virus does not necessarily produce an interstitial infiltration of mononuclear cells even when present in high concentration and when producing a severe infection, for in the cases without interstitial changes the inclusion bodies are present in greater abundance than in the other cases, and are especially numerous immediately about the bronchi, as fig. 4 illustrates.

In the present series of cases of children dying with whooping-cough, therefore, there are instances in which (1) the interstitial change is present when only the Bordet-Gengou bacillus could be cultivated; (2) the interstitial change is present when the influenza bacillus but not the Bordet-Gengou bacillus was present; (3) the interstitial change

is present in lungs showing no inclusion bodies in the epithelium; (4) the interstitial change is present in lungs showing inclusion bodies, (5) the interstitial change is absent in lungs showing great numbers of inclusion bodies. Thus, as for the etiological agent responsible for the interstitial change (which, in spite of its occasional absence, is nevertheless the most constant pathological lesion of pertussis) there are arguments against the Bordet-Gengou bacillus (its absence in cases when the interstitial change is present), against the influenza bacillus (the absence of the interstitial change in some cases of influenza-bacillus infection, and the failure of this bacillus to cause the interstitial change in experimental infection), and against a filterable virus (the presence of abundant intranuclear inclusions in the absence of the interstitial change). These cases show that the peculiar mononuclear-cell infiltration may be absent when any one of the possible bacterial causes is present, and may be present when any one of them is absent; and they emphasize the fact that the origin of the peculiar mononuclear-cell infiltration is not yet perfectly clear, in spite of statements ascribing it to the influenza bacillus or to the Bordet-Gengou bacillus.

In this discussion we have examined fairly the view that pertussis may be primarily due to a filterable virus which paves the way for the secondary invasion of the Bordet-Gengou bacillus and the influenza bacillus, the latter organisms becoming chiefly responsible for the cough because of their tendency to localize in the cilia of the respiratory tract. On the basis of the observations presented in this paper we were led to carry out a series of experiments on chimpanzees in collaboration with Dr. Long, Dr. Holt, and Dr. Brown. These experiments, which are described in a separate report, provide definite evidence that there is present in the blood, and in the bacteria-free, filtered tracheal secretions of children with pertussis, a virus capable of producing a catarrhal condition of the upper respiratory tract accompanied by fever, which closely resembles the first stage of whooping-cough. This virus, however, has not yet been proven to be distinct from the virus of the common cold. On the other hand, large doses of Bordet-Gengou bacilli alone have produced in some of the animals a condition resembling pertussis clinically (paroxysmal cough, lymphocytosis). The significance of these findings is discussed in that

communication. It is hoped that further experiments, to be carried out during the coming pertussis season, may serve to clarify the problem.

SUMMARY

1. The present state of the evidence is insufficient to command the belief that the Bordet-Gengou bacillus represents the whole story of the etiology of whooping-cough.

2. It is shown that influenza bacilli localize in the cilia of the respiratory tract exactly as do Bordet-Gengou bacilli. They are found in this location when they act as secondary invaders, not only in pertussis but also in influenza and in measles. The presence of Gram-negative bacilli in the cilia in pertussis does not mean, therefore, that they are Bordet-Gengou bacilli. The relation of the influenza bacillus to paroxysmal cough is discussed.

3. The mononuclear-cell infiltration of the bronchial walls which is characteristic of interstitial pneumonia occurs in pertussis uncomplicated by pneumonia. It is pointed out that this interstitial change occurs almost exclusively in diseases in which there are strong reasons for suspecting the etiological rôle of filterable viruses (measles, influenza, pertussis), and the possibility that this lesion may be the effect of an invisible virus rather than of secondary bacterial invaders is discussed.

4. Observations bearing on the view that an invisible virus may play a rôle in the etiology of pertussis are presented. Cases showing intranuclear inclusion bodies in the lungs in cases of pertussis are described, and the possibility that these may represent the effect of aspirated herpes virus is discussed. Experiments which have demonstrated the existence of a filterable virus associated with pertussis, and capable of producing respiratory catarrh, are reported in a separate communication, together with evidence relating to the rôle of the Bordet-Gengou bacillus.

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FIG. 1. Lung from case of pertussis dying with convulsions 5 days after onset of cough. There was no pneumonia, but the bronchial walls are densely infiltrated with mononuclear cells exactly as they are in "interstitial pneumonia." The influenza bacillus was cultivated from the lung (Autopsy 9610).

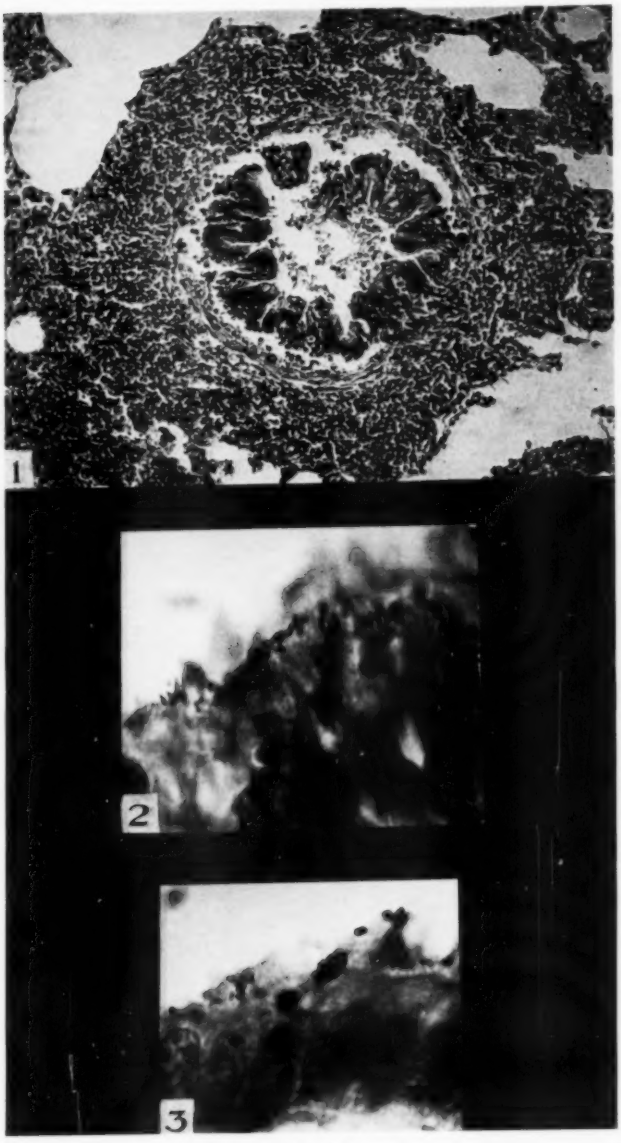
(Photographs by Mr. Milton Kougl).

FIGS. 2 AND 3. Show the localization of influenza bacilli in the cilia of the bronchi, in the lung of a child two months old who contracted measles from its mother and died from pneumonia several days after the appearance of the rash. The influenza bacillus was grown from the lung. The section is stained with Gram's stain and the bacilli are red. In figure 3, the dark masses in the cilia to the right of the median line of the photograph are clumps of influenza bacilli. Individual bacilli are more clearly seen to the left (Autopsy 6199).

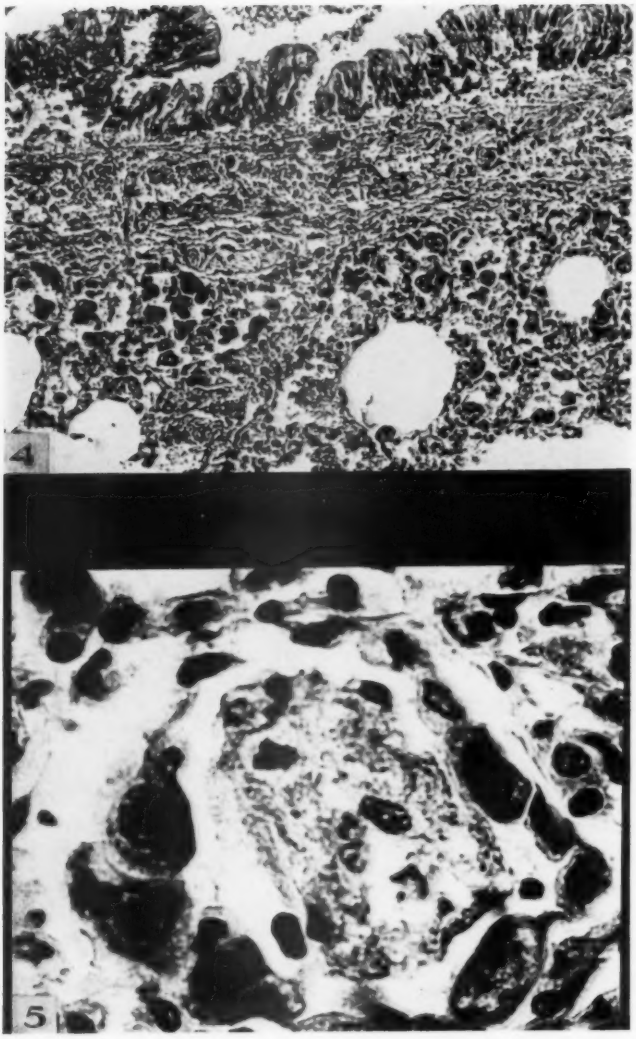
FIG. 4. Lung of a child who died five weeks after the onset of pertussis. There can be seen many greatly enlarged alveolar epithelial cells containing intranuclear inclusions in the alveoli immediately about the bronchial wall, but there is no characteristic interstitial mononuclear-cell infiltration. The bronchial wall contains a few scattered leucocytes and only a rare mononuclear cell (Autopsy 9122).

FIG. 5. Shows the enlargement of the lining cells of an alveolus in the same case as figure 4. Intranuclear inclusions are visible in three of the enlarged cells at the left.

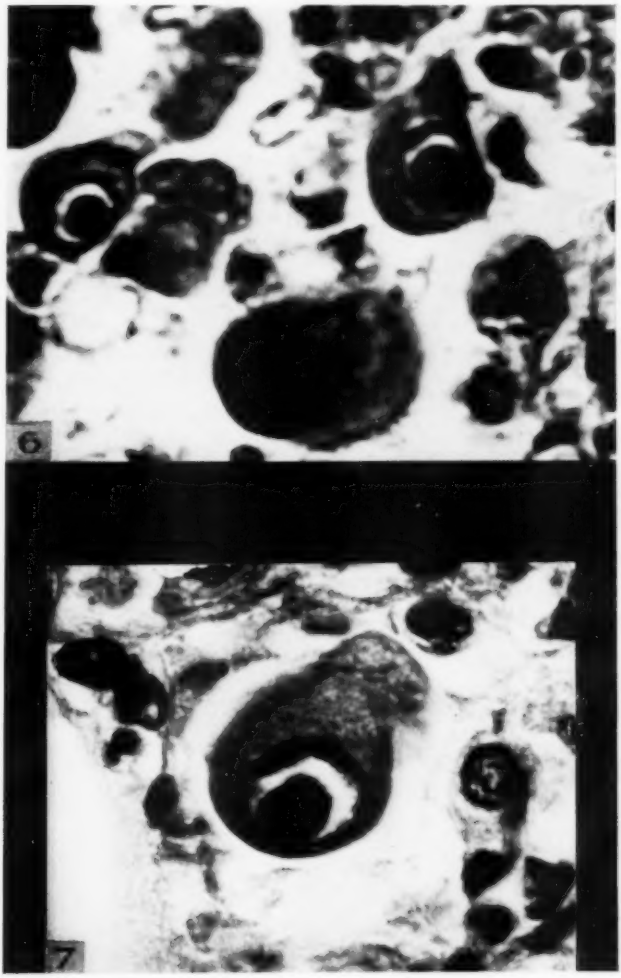
FIGS. 6 AND 7. Intranuclear inclusions characteristic of those seen in autopsies of children with pertussis (Autopsies 8586, 8644, 8805, 8820, 9122).



FIGS. 1-3



FIGS. 4 AND 5



FIGS. 6 AND 7

THE SPLENIC LESION IN HEMOLYTIC JAUNDICE[1]

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During the past few years we have been interested in the different groups of diseases associated with splenomegaly. One of the obvious lines of investigation has been the examination of the microscopic sections of the spleens from these different groups of cases, which have been either removed at operation or have appeared at autopsy. We have been particularly fortunate in having not only a large amount of pathological material available for study but also, in most instances, the clinical records of the patients, or the patients themselves. In addition to the material observed at this hospital, we were permitted to study the available spleen sections collected, during the past twenty years, at the Johns Hopkins Hospital in Baltimore.

The diseases studied include splenic anemia, hemolytic jaundice, purpura hemorrhagica, Gaucher's disease, various leukemias and many other cases of unknown diagnosis. During the course of this study, it soon became apparent, both here and in Baltimore, that the majority of the spleen sections failed to show sufficiently obvious changes to permit definite classification. However, one or two of the disease groups presented such definite and constant changes in the microscopic appearance of the spleen that we came to recognize these changes as being characteristic.

Among the diseases that present uniformly characteristic variations from the normal in the spleen, in addition to the leukemias and Gaucher's disease, belongs sickle-cell anemia. This pathological picture has recently been described in detail by Rich in the Johns Hopkins Hospital Bulletin (1). We feel that the pathological picture as described by him is readily recognizable in routine sections of the spleen and is diagnostic of this condition.

It is the change found in the spleens of patients presenting the

[1] Received for publication September 16, 1932.

clinical picture of hemolytic jaundice that has been of particular interest to us during this work.

The microscopic appearance of these spleens has, on several occasions, been described. The first available description is that of Vaquez and Giroux (2) in which the spleen of hemolytic jaundice is described as being markedly "congested." This "congestion" is referred to again in a report of one case by Dick (3) who called attention to the blood-filled pulp, the dilated sinuses and the small follicles. He stressed the absence of visible phagocytosis of the red cells and the rather startling absence of blood pigment. There is a report by Houcke (4) of one case showing the changes described by Dick, and Dr. W. D. Newcomb, in examining the spleen of one of the cases reported by Lord Dawson of Penn (5) mentions the same features. In addition, Eppinger (6) gives the pathological changes seen in these cases and in Boyd's (7) recent textbook the microscopic changes found in this disease are briefly mentioned. It is, therefore, obvious that this microscopic picture is known. It seems, however, that the characteristic microscopic pathology of hemolytic jaundice has never been sufficiently emphasized and has never been described as a definite pathological entity. We feel, from our study of the spleen of thirty cases of this disease, that the lesions found are constant and that a diagnosis of hemolytic jaundice may be made from the study of the microscopic sections alone.

Thirty cases presenting the clinical symptoms of hemolytic jaundice have now been studied. In these thirty cases of typical hemolytic icterus, microscopic examination of the spleen has revealed, in all instances, the same definite and characteristic changes.

In addition to this group we have examined the spleens of six cases of so-called "atypical" hemolytic jaundice, as well as a large number of spleens from cases of Banti's disease, purpura, and other conditions associated with splenomegaly. As a control group the spleens from two hundred consecutive autopsies were studied here and a similar number were studied in the Pathological Laboratory at the Johns Hopkins Hospital.

The six spleens from patients with "atypical" acquired hemolytic jaundice showed a variety of changes in no way similar to those of the typical hemolytic jaundice group, or even to each other. Of all the

sections examined from all the different groups of splenomegalies only two presented the characteristic features of hemolytic jaundice and both of these, as will be described in detail later, were from patients subsequently found to have hemolytic jaundice. Of the four hundred "control" spleens only one was found that was characteristic of hemolytic jaundice. This was from a patient dying with an acute illness who had, however, during her short stay in the Johns Hopkins Hospital, an unexplained splenomegaly. The diagnosis of hemolytic jaundice was recorded by the Pathological Department in their final anatomical diagnosis. From the review of this pathological material and from an analysis of the clinical records of these thirty cases of hemolytic jaundice we have come to the conclusion that hemolytic jaundice is a definite clinical and pathological entity.

The clinical features are characterized by a long-standing, low-grade hemolytic type of anemia, with mild, variable jaundice and splenomegaly. Although it does occur at times in more than one member of the same family, the familial or congenital aspects of any given case are not necessary to the diagnosis. That the disease is usually very mild is well known and there is no reason for not assuming that a form exists in which noticeable symptoms fail to develop for many years. Typical cases have been seen here and elsewhere whose symptoms have not appeared until the fourth or fifth decade of life, and these cases are identical in all respects with the so-called congenital forms. In addition, there are on record examples of this disease in latent form, found in families, one of whose members had the active disease (8), (9).

The blood of these patients shows a moderate, variable anemia, with normal white count and normal platelet count. The reticulocytes are markedly increased in all instances, ranging usually from 15 to 50 per cent, and occasional normoblasts are seen. The majority of the red cells are microcytes and the presence of the microcytes is, we feel, a necessary feature in the diagnosis. In all of these cases there has been an alteration in the fragility of the red blood cells which persists, together with the microcytosis, after splenectomy. There is a moderately elevated serum bilirubin, giving the indirect Van den Bergh reaction, and there is a definite increase in urobilin excretion. In all of the cases of patients who have consented to operation, splenectomy has resulted in a complete and permanent

symptomatic cure. It is of interest, perhaps, that splenectomy in the atypical cases has been of only very slight and transient benefit or none at all.

The spleen of the typical hemolytic jaundice case is enlarged, weighing between 1000 and 1500 grams. It is usually easily removable at operation, being relatively free from adhesions. On section the fresh spleen presents a uniform and fairly characteristic appearance. The cut surface is relatively dry and it is of a dark purplish-red color, homogeneous in texture, bulging slightly above the capsule. The Malpighian bodies are not seen.

The microscopic appearance is uniform in all instances. The Malpighian bodies are small and widely separated. The venous sinuses are enlarged, widely dilated and frequently empty. The sinus endothelium is prominent, the outline of these cells often bulging into the lumina of the sinuses. The pulp is a mass of closely packed red cells and this diffuse infiltration is the most striking feature of the microscopic appearance. There is no increase of connective tissue and no visible increase of iron pigment. The so-called iron incrustations are frequently encountered lying usually within the trabeculae. There is no visible evidence of phagocytosis of the red cells and, except for an occasional lymphocyte, one finds nothing but red cells distending, distorting and dilating the pulp.

In two recent instances our interpretation of these changes has been justified by actual test. In the first instance, a section of spleen was found, removed twelve years ago at operation. The diagnosis at that time was pernicious anemia. The spleen presented to us the characteristic features of hemolytic jaundice. We were able to find the patient and discovered that she had been slightly jaundiced and anemic for fourteen years before the operation and that all symptoms had disappeared following the surgical procedure. In addition, this patient has a sister who has had the typical clinical picture of hemolytic jaundice for more than thirty years, together with all the usual confirmatory laboratory tests. The other case is that of a woman whose spleen was removed in 1912. A diagnosis of splenic anemia was made at that time and the pathologists, in examining the sections of the organ, made a definite diagnosis of Banti's disease. When, recently, the patient, who had been completely symptom-free since operation, pre-

sented herself to the surgeon who had removed the spleen, he was informed that her daughter was developing the same syndrome. On re-examination of the old frozen section, the spleen presented the features described as being typical of hemolytic jaundice. In addition, her daughter presents the complete picture of this disease, the microscopic examination of the daughter's spleen showing the same identical changes.

SUMMARY

Thirty cases of hemolytic jaundice have been studied. All presented the same clinical features and all presented the same microscopic appearance in the spleen.

In a large series of controls only two spleens were found that presented the pathological features of this disease. In both these cases subsequent clinical investigations showed that these two patients had typical hemolytic jaundice. In both of these instances the diagnosis was first made by finding the characteristic features in the microscopic examination of the spleen.

It is felt that hemolytic jaundice is a definite clinical and pathological entity and that no difference exists between the congenital and acquired types of the typical disease. From a limited study of six cases of "atypical" acquired hemolytic jaundice it appears that the cases included in this group bear no relation to typical hemolytic jaundice or even to each other.

CONCLUSIONS

Hemolytic jaundice is a definite clinical and pathological entity. The diagnosis may be made from microscopic examination of the spleen.

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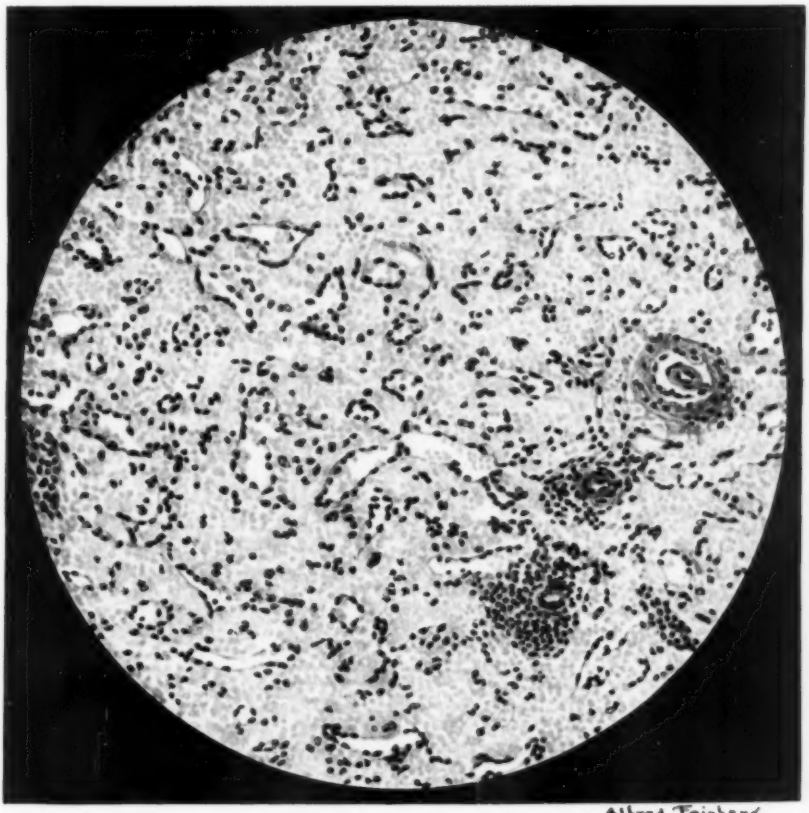
PLATE 1

A water-color painting of a Hemolytic Jaundice Spleen showing the dilated sinuses, the prominent sinus endothelium, the small follicles and the blood-filled pulp. 8 mm. Apochromatic objective, 5x ocular.


Alfred Feinberg

PARATYPHOID-LIKE FEVER IN CHILDREN DUE TO THE SALMONELLA SUIPESTIFER GROUP[1, 2]

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Infections in man with bacilli of the hog cholera group, *Salmonella suipestifer*, have been comparatively rare in this country. During the war numerous cases of infection with a bacillus closely allied to the hog cholera bacillus, known as paratyphoid C, were reported in Eastern Europe and Asia. This organism, however, differs from B. suipestifer culturally and, as far as we know, has not been isolated in America. Paratyphoid C is not associated with disease in animals. The group of Salmonella suipestifer, with which we are concerned in this paper, consists primarily of animal pathogens, which occasionally give rise to disease in man.

B. suipestifer infections in man have been most often associated with food poisoning due to the ingestion of uncooked pork in the form of sausage or smoked ham, especially in Germany. It is noteworthy, however, that there have been a small number of epidemics due to foods other than pork, and in which the relation to infected pigs is vague or entirely lacking. Thus in Germany, one of the most carefully studied outbreaks (1), involving 103 individuals, was due to ice cream contaminated with B. suipestifer. In the original communication on this epidemic, it was thought that the woman who made the ice cream was a B. suipestifer carrier. This finding (2) was, however, not confirmed. In this country one of the larger outbreaks (150 persons) (3) was shown to be due to unpasteurized milk. In this instance no evidence was obtained that any of the personnel of the dairy were B. suipestifer carriers or that there were any sick pigs in the vicinity. A small outbreak in one family (4) was shown to be due

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to tapioca pudding in which B. suipestifer was demonstrated. The only possible source of the organism in this instance was thought to be contamination of the cook's hands by handling pork, bought on the same day that the tapioca pudding was prepared.

Although B. suipestifer is usually associated with acute gastro-enteritis, a small number of sporadic cases have been reported in adults in recent years (5), presenting a varied clinical picture in which B. suipestifer was isolated by blood culture. A few infections with B. suipestifer have also been observed in children.

Nabarro *et al.* (6), in England in 1929, cultured B. suipestifer from the joints of two children with arthritis. A report of a mild paratyphoid-like fever in a 6-year-old child, from whom B. suipestifer was isolated by blood culture, was sent to us by Haynes from Indianapolis (7). This patient lived on a farm, where cases of hog cholera had occurred, so that this is one of the few cases in which the source of infection is fairly definite. Ten Broeck (8) reported a similar case in a 6-year-old Chinese child, except that in his case no source of infection was found. A fatal febrile illness in an infant of 7 months due to B. suipestifer, has recently been reported from Germany by Rau (9). The patient was of good family, lived in a city and was well taken care of. Both parents were in good health. The onset was sudden with fever, vomiting and epistaxis. The second day diarrhea set in, and fever (104°F.) and diarrhea continued throughout the 24 days of illness. B. suipestifer was isolated from the blood and from the urine, but not from the stools. The spleen was not enlarged. The leucocytes were 6,800 with 46 per cent polymorphonuclears. No possible source of infection was found. No autopsy was obtained.

From a brief survey of the literature, the number of cases of infection with B. suipestifer in children has been sufficiently small and sporadic to warrant reporting 7 cases which occurred at the Harriet Lane Home, Johns Hopkins Hospital, during the winter of 1931–1932.

Case 1. L. K. (No. 75027) a 6-year-old colored girl, who lived in the country, was admitted 11/4/31 because of acute abdominal pain. The patient's mother had had gonorrhea for 3 years, and the patient herself had also a slight vaginal discharge. She was well until four days before admission, when she seemed drowsy. Three days before admission she began to complain of abdominal pain, which continued with increasing severity until the day of admission. The night before admission she developed fever and began to vomit. The day of admission she complained of headache and her nose began to bleed.

Physical examination on admission: The patient seemed acutely ill, toxic, temperature 104°F., epistaxis, foul breath; lungs clear, heart negative, board-like

abdomen, non-specific vaginal discharge, urine negative, W. B. C. 30,000. The following diagnostic possibilities were considered: (1) ruptured appendix; (2) perforated typhoid ulcer; (3) gonococcal peritonitis. An immediate laparotomy showed a normal appendix and a small amount of fibrous pus in the pelvis. The surgeon's impression was gonococcal peritonitis.

The patient's temperature failed to subside after operation and a blood culture (11/7/31) was positive for B. suipestifer (Group II). The temperature remained high for 14 days and then came down gradually. No diarrhea. Serum taken 11/23 failed to agglutinate typhoid, paratyphoid A or B or the homologous organism. Stool cultures were repeatedly negative. Wassermann negative. The patient was discharged in good condition, 12/1/31, after 28 days in the hospital.

Case 2. P. Y. (No. 70314) an 11-month-old colored boy, living in Baltimore, was admitted 11/16/31 with a diagnosis of typhoid fever. The patient had had nasal diphtheria, otitis media and pertussis during the first six months of life. He had been well until four days before admission, when he awoke with a cough and high fever. The main symptoms were fever and anorexia. He was somewhat constipated. He became increasingly drowsy and twitching movements were observed, but no real convulsions.

Physical examination on admission: Temperature 104.9°, drowsiness, delirium, meningismus; lungs clear, heart negative, pulse 140, frequent jerking movements of the extremities, full abdomen, liver enlarged, spleen not felt.

Laboratory findings: Hemoglobin 46 per cent, W. B. C. 7,840, polymorphonuclears 42 per cent, mononuclears 58 per cent, urine negative except for ++ albumin. Lumbar puncture (11/17), negative. First blood culture (11/16) positive for B. suipestifer (Group II), second blood culture (11/18) positive for B. suipestifer. Serum obtained 11/17; negative agglutination x typhoid, paratyphoid A and B, positive x homologous culture in a dilution of 1 to 80. Urine culture negative 11/21. Repeated stool cultures negative. Wassermann negative.

The temperature ranged from 105 to 103° for 4½ days, falling to 100.4° on the fifth. The patient remained somewhat delirious for eight days after his temperature was normal. No diarrhea. The patient was in the hospital 19 days, and was discharged in good condition 12/3/31.

Case 3. D. S., (No. 75064) a 9-month-old white male infant, living in Baltimore, was admitted 12/2/31 with a diagnosis of congenital lues and syphilitic meningitis. The mother of the patient had a positive Wassermann. The patient had had a rash at the age of 2 months. He was seen by a doctor at that time who advised "needle treatments." At the age of six months a Wassermann was taken, and he received three antisyphilitic treatments. The mother, however, was of the opinion that the injections made the patient sick, and discontinued further treatments about two months before admission. At the age of 9 months he could not sit alone. No cod-liver oil or orange juice had been given. Three days before admission the patient would not hold his head up and the mother thought that his

back hurt. He refused food and had fever. No diarrhea. He failed to improve and was admitted to the hospital.

Physical examination on admission: Temperature 103.6°, coated tongue, lungs clear, heart negative, pulse rapid, enlarged liver and spleen.

Laboratory findings: W. B. C. 9,200, 66 per cent PMN., 34 per cent mononuclears. Lumbar puncture (12/3) negative. Blood cultures taken 12/3 and 12/6 both positive for B. suipestifer (Group II). Serum obtained 12/13 failed to agglutinate typhoid, paratyphoid A or B or the homologous organism. Stool culture (12/15) was positive for B. suipestifer. The Wassermann was strongly positive.

The temperature fell to 100.4° in about six days. No diarrhea. The patient did not eat well and lost weight which he gained back very slowly. He was discharged 12/30 after 27 days in the hospital.

Case 4. F. C. (No. 72923) a 7-month-old colored female infant, living in Baltimore, was admitted 12/13/31 because of suspected typhoid fever. The patient came of a tuberculous family. She had had several attacks of otitis media. Five days before admission she again developed otitis media; three days before admission her appetite became poor. On the day of admission she had fever and a chill, and vomited once. She had been in contact with a family in which there was a case of typhoid fever.

Physical examination on admission: Temperature 104°, purulent right otitis media, lungs essentially clear, heart negative, abdomen distended, spleen enlarged.

Laboratory findings: W. B. C. 9,200 with 44 per cent PMN. and 56 per cent mononuclears. Urine negative. Blood culture (12/13/31) positive for B. suipestifer (Group I). Serum obtained 12/15 failed to agglutinate typhoid, paratyphoid A or B, but agglutinated the homologous culture in a dilution of 1 to 320. Repeated urine and stool cultures negative. Wassermann negative.

The temperature fell in 3 days and then remained normal. No diarrhea. The disease ran a mild course, and the patient was discharged in good condition 12/27/31, after 15 days in the hospital.

Case 5. G. J. (No. 75462) a 4-year-old colored girl, living in Baltimore, was admitted 12/21/32 with a diagnosis of capillary bronchitis and pertussis. The patient had had pertussis nine weeks before admission. She recovered slowly. Four days before admission, she developed fever, coughed a little, complained of abdominal pain and would not eat. No vomiting, bowels normal. She did not improve and was, therefore, admitted.

Physical examination on admission: Temperature 104.3°, respirations 46 with dilation of the alae nasi, acute tonsillitis and pharyngitis, bronchitis with patches of bronchopneumonia at right base; heart negative, pulse 136, abdomen negative, spleen not felt.

Laboratory findings: Urine negative. W. B. C. 8,000, PMN. 70 per cent, 29 per cent mononuclears. X-ray (12/22) showed pneumonia at right base. Wasser-

mann negative. Blood culture (12/22) positive for B. suipestifer (Group II). Serum taken 1/4/32 failed to agglutinate typhoid, paratyphoid A and B or the homologous culture. Repeated stool cultures were negative.

The temperature dropped gradually in 5 days and the râles in her lungs disappeared. She was discharged 1/5/32, after 16 days in the hospital.

Case 6. C. M. (No. 76379) a 5-year-old colored girl, living in Baltimore, was admitted 2/20/32 with a diagnosis of typhoid fever. Her past history was negative. The patient had been well until six days before admission, when she complained of abdominal pain and seemed to have fever. Her appetite was poor. Five days before admission, she vomited and continued to vomit once or twice a day until admission. Her chief complaint continued to be abdominal pain.

Physical examination on admission: Obviously ill. Temperature 103.6°. Meningismus, dirty mouth, lungs clear, heart negative, pulse 112, full abdomen, liver and spleen not felt.

Laboratory findings: W. B. C. 4,750, PMN. 49 per cent, mononuclears 51 per cent. Wassermann negative. Blood culture 2/20 positive for B. suipestifer (Group II). Serum obtained 2/29 failed to agglutinate typhoid, paratyphoid A or B or the homologous organism. Repeated stool and urine cultures negative.

The patient's temperature fell to normal on the fourth day. She tended to be constipated during her stay in the hospital. She was discharged in good condition 3/9/32 after 20 days in the hospital.

Case 7. G. M. (No. 72933) a 4-year-old colored girl, living in Baltimore, was admitted 2/25/32 with a diagnosis of typhoid fever. The past history was negative, except for frequent colds and chronic tonsillitis. She had been well until 2/21, when she complained of abdominal pain and seemed apathetic. 2/22 she had a temperature of 105°. The fever and abdominal pain continued. 2/29 she vomited twice.

Physical examination on admission: Temperature 103.6°, coated tongue, foul breath, lungs clear, heart negative, pulse 132, abdomen distended, spleen not felt, urine negative.

Laboratory findings: W. B. C. 7,800, PMN. 66 per cent, mononuclears 34 per cent. Wassermann negative. Blood culture taken 2/25 was positive for B. suipestifer (Group II). The temperature gradually fell and became normal on the fifth day. No diarrhea. Serum taken 2/29 failed to agglutinate typhoid, paratyphoid A or B or the homologous organism. Repeated stool cultures were negative.

The patient made an uneventful recovery and was discharged in good condition 3/10/32 after 14 days in the hospital.

Source of infection. As far as we have been able to determine, none of these patients had any contact with each other. The parents of two of them (cases 2 and 3) gave a history of having had a febrile illness

resembling that of their children. The serum of one of them agglutinated the organism isolated from her son (case 3), and also that of one of the other patients. The serum of the other parent failed to agglutinate the bacillus isolated from his son or any other strains of B. suipestifer. In case 2 a single stool examination of one of the parents was negative for B. suipestifer. Six of the children lived in the city of Baltimore and only one lived in the country. The youngest child was seven months, the oldest 6 years. Six of the seven children were colored; three of the cases occurred in infants less than 1 year of age.

Symptoms. The onset was usually abrupt, the most common symptoms being anorexia and fever. In the older children, abdominal discomfort was one of the complaints. Occasional vomiting occurred in four of the children, epistaxis occurred once. In none of the cases was diarrhea a feature. A chill was observed in one case only.

Physical findings. The most striking findings were hyperpyrexia, drowsiness, meningismus and foul breath. The abdomen was usually described as "full," the spleen was palpable in only two of the children, one being the congenital luetic. In no instance were rose spots observed.

White blood count. All the patients, except case 1 who was submitted to the emergency operation, had low white counts. One patient (case 5), who had bronchopneumonia, had a white count of 8,900 with 70 per cent polymorphonuclears. The white counts of the five patients ranged from 4,750 to 9,200 with polymorphonuclears from 43 per cent to 66 per cent.

Diagnosis. The diagnosis in every case depended on the isolation of the organism by blood culture. Two of the seven patients gave two positive blood cultures. Only two agglutinated the homologous cultures during their stay in the hospital (cases 2 and 4). The sera were not tried against other strains of suipestifer at this time. They uniformly failed to agglutinate typhoid and paratyphoid A and B. In spite of repeated stool cultures, B. suipestifer was isolated in only one case (case 3). All urine cultures were negative.

Course. The temperature in the uncomplicated cases fell on the 2nd to the 5th day, and the patients all made uneventful recoveries. The course was mild, and there were no recurrences or complications. The patients remained in the hospital from 14 to 29 days.

Bacteriology. The organisms isolated from these cases were Gram-negative motile bacilli, which gave the cultural reactions of paratyphoid B in that they failed to ferment lactose and saccharose, and fermented glucose, mannite, xylose, and rhamnose with the production of gas. They differed from paratyphoid B, in not fermenting arabinose, trehalose and inosite. The fermentation of dulcite was delayed and irregular. At the time that these cultures were isolated, no sera were on hand for complete identification. We, therefore, sent them to Dr. McCoy of the National Health Institute who identified them as B. suipestifer. The cultures were also sent to Dr. Ten Broeck of the Rockefeller Institute for Animal Pathology, who pointed out to us that these strains fell into two groups, six of them belonging to B. suipestifer, Group II, and one to B. suipestifer, Group I. He kindly sent us known hog-cholera strains belonging to both groups, for comparison, and also some Group II suipestifer serum.

B. suipestifer was first divided into two groups by Andrewes and Neave (10), in 1921. These workers showed by means of absorption tests that Group I suipestifer will exhaust the agglutinins from both Group I and Group II suipestifer sera, but Group II will exhaust only Group II sera and leave the specific titer of Group I sera undiminished. Members of Group I are, therefore, diphasic since they contain two types of antigen: one, the non-specific antigen which is common to both groups, the other, the specific antigen, which is characteristic of Group I. Members of Group II contain only the group antigen, and are, therefore, monophasic or non-specific. Group I suipestifers, furthermore, differ from Group II in failing to produce hydrogen sulphide in lead acetate media. Strains of suipestifer isolated in Western Europe usually belong to Group II, and Group I suipestifer represents the so-called American type of hog-cholera bacillus, first described by Theobald Smith. In recent years, however, organisms belonging to Group II have been isolated from infected pigs and from man in this country, and Nabarro *et al.* (6) have reported two cases of human infection with Group I in England, so that the difference in the distribution of the two groups is not very clear cut. Paratyphoid C, the organism isolated in Eastern Europe and China, is identical serologically with the diphasic Group I suipestifers, but differs from B. suipestifer in fermenting arabinose and trehalose.

The cultural differences between paratyphoid B. and the suipestifers

of porcine and human origin are shown in table I. The difference between the hydrogen sulphide production of the two groups of suipestifer is also included.

Agglutination. A rabbit was immunized with Culture I (case 4) (Group I) and another rabbit with culture E (Case 3) (Group II). Two rabbits were also immunized with a known diphasic hog-cholera culture A, and a known monophasic hog-cholera culture C.

In order to obtain a pure diphasic serum, the diphasic cultures were

TABLE 1

CULTURES	ARABINOSE	DULCITE	INOSITE	TREHALOSE	LEAD ACETATE
A.* Hog cholera 16 (diphasic)	−	−	−	−	−
B. Suipestifer 692 (diphasic)	−	−	−	−	−
C. Suipestifer 678 (monophasic)	−	−	−	−	+
D. Suipestifer 606 (monophasic)	−	±	−	−	+
E. Case 3 (blood culture)	−	±	−	−	+
F. Case 3 (stool)	−	±	−	−	+
G. Case 1 (blood culture)	−	±	−	−	+
H. Case 5 (blood culture)	−	±	−	−	+
I. Case 4 (blood culture)	−	−	−	−	+
J. Case 2 (blood culture)	−	±	−	−	+
K. Case 7 (blood culture)	−	−	−	−	+
L. Case 6 (blood culture)	−	±	−	−	+
Paratyphoid B	+	+	+	+	+

+ = Fermentation with gas production within 24–48 hours in the case of the sugars, and blackening of the medium in case of the lead acetate.

− = No change after 7 days' incubation, ± = delayed fermentation beginning the 5th or 6th day.

* Cultures A, B, C, D were isolated from pigs and sent to us by Dr. Ten Broeck.

separated into the specific and non-specific forms according to the method of Andrewes (11). This author found that diphasic cultures of the Salmonella group were not homogeneous antigenically speaking, but consisted of two well defined types of bacilli, one representing the group antigen, the other the specific antigen. These types are unstable and keep changing from one into the other, so that their relative proportion in a mass culture at any one time is uncertain. In order to obtain a pure specific serum, only bacilli of the specific type could be used for injection.

Specific forms of culture A, hog cholera 16 (diphasic) and culture I (case 4) were prepared as follows: the cultures were streaked and isolated colonies fished to broth. These broth cultures were grown in a short time, 10 to 12 hours, and 1 drop of formalin was then added. These formalized cultures were agglutinated with the known monophasic suipestifer serum (non-specific), kindly sent to us by Dr. Ten Broeck. A striking difference in the reaction of the various cultures was noted: Some agglutinated well, and others were completely negative. The cultures that agglutinated with this serum were known to represent the non-specific phase and were, therefore, discarded for purposes of immunization. The ones that failed to agglutinate were combined and considered to represent the specific phase. The latter were used for injection.

TABLE 2

Serum no. 269, prepared with the specific type of culture I (Case 4)

STRAINS	DILUTIONS USED					
	1,000	2,000	4,000	6,000	10,000	Controls
A, specific	3+	3+	+	−	−	−
A, non-specific	−	−	−	−	−	−
B, specific	4+	4+	−	−	−	−
B, non-specific	−	−	−	−	−	−
I, specific	2+	4+	4+	4+	2+	−
I, non-specific	−	−	−	−	−	−
Permanently non-specific C	−	−	−	−	−	−
Permanently non-specific D	−	−	−	−	−	−
Permanently non-specific E	−	−	−	−	−	−
Permanently non-specific F	−	−	−	−	−	−
Permanently non-specific G	−	−	−	−	−	−
Permanently non-specific H	−	−	−	−	−	−
Permanently non-specific J	−	−	−	−	−	−
Permanently non-specific K	−	−	−	−	−	−
Permanently non-specific L	−	−	−	−	−	−
Paratyphoid B	−	−	−	−	−	−

Agglutinations incubated two hours at 56°C. and read after standing overnight in the icebox. Young formalinized broth cultures were used as antigens.

Each rabbit was given three intravenous injections of the formalinized cultures at weekly intervals. In the case of the monophasic strains, C (hog cholera 678) and E (case 3), young formalinized mass cultures were used.

As seen by the following charts, serum No. 269 obtained from the rabbit immunized with the specific type of culture I (case 4) agglutinated the homologous specific type, but not the homologous non-

specific type. It also agglutinated the specific types, but not the non-specific types of the diphasic porcine cultures A and B. It failed to agglutinate the cultures isolated from the other six cases and the two porcine monophasic strains C and D.

The agglutinations of these strains with serum no. 267 prepared with the specific type of the porcine diphasic culture A gave essentially the same results and are, therefore, not recorded.

TABLE 3

Serum no. 270, prepared with the whole culture E (Case 3)

STRAINS	DILUTIONS USED					
	1,000	2,000	4,000	6,000	10,000	Controls
A, specific	−	−	−	−	−	−
A, non-specific	4+	4+	2+	2+	−	−
B, specific	−	−	−	−	−	−
B, non-specific	4+	4+	4+	3+	+	−
I, specific	−	−	−	−	−	−
I, non-specific	4+	3+	3+	+	−	−
Permanently non-specific C	4+	4+	4+	4+	3+	−
Permanently non-specific D	4+	4+	3+	3+	+	−
Permanently non-specific E	4+	4+	3+	3+	2+	−
Permanently non-specific F	3+	3+	3+	2+	+	−
Permanently non-specific G	2+	3+	3+	3+	2+	−
Permanently non-specific H	2+	3+	4+	4+	3+	−
Permanently non-specific J	4+	4+	4+	2+	−	−
Permanently non-specific K	4+	3+	2+	2+	−	−
Permanently non-specific L	4+	4+	3+	3+	−	−
Paratyphoid B	−	−	−	−	−	−

The agglutinations of these strains with serum no. 269 prepared with the porcine monophasic culture C corresponded closely to those recorded above and are, therefore, not recorded.

Serum No. 270 prepared with culture E, (case 3) agglutinated the homologous culture and the cultures from all the other cases except the specific type of culture I (case 4). It agglutinated the porcine monophasic strains C and D, and the non-specific types of the diphasic porcine strains A and B, but not the specific types of A and B.

These agglutinations indicate that six of the cultures isolated from these cases are monophasic (non-specific) and that one (case 4) is diphasic.

Absorptions. These findings were further confirmed by absorption tests. When serum No. 269 was absorbed with the specific type of the homologous culture, all the agglutinins were removed for the homologous specific type and for the specific type of the porcine culture A. The titer for the homologous and heterologous specific types was only slightly diminished by absorption with non-specific type of the homologous culture, and not at all diminished by absorption with the monophasic culture E.

Method: 0.5 cc. of serum was absorbed with the sediment from 100 to 200 cc. of formalinized culture which was suspended in 4.5 cc. of saline, making a dilution of 1 to 10. The suspension was incubated at 40 to 42°C. for 3 hours and allowed to stand in the ice-box over night. Dilutions were then made from the supernatant fluid.

TABLE 4

Serum no. 269 immunized with the specific type of culture I (Case 4)

CULTURE	ABSORBED WITH									CONTROL		
	Specific type of I			Non-specific type of I			Monophasic culture E					
	500	1,000	2,000	500	1,000	2,000	500	1,000	2,000	500	1,000	2,000
I, specific	−	−	−	2+	2+	+	3+	4+	3+	3+	3+	2+
A, specific	−	−	−	2+	2+	+	3+	4+	+	3+	3+	2+

The absorption of serum No. 270 with the homologous or a heterologous monophasic strain, or with the non-specific type of culture I, removed all the agglutinins for the homologous and heterologous monophasic strains and for the non-specific type of culture I. The absorption with the specific type of culture I did not reduce the titer for the homologous or heterologous monophasic cultures, or for the non-specific type of culture I.

Virulence. The virulence of the hog-cholera bacillus for rabbits on subcutaneous injection was first observed by Theobald Smith, and is a striking and constant characteristic of these organisms, even after prolonged artificial cultivation. The monophasic and diphasic strains of Salmonella suipestifer of porcine origin are apparently equally virulent. Ten Broeck *et al.* (8) tested the virulence of the cultures isolated by them from cases in China, and found that members of the

monophasic Group II seemed to be just as virulent as the porcine strains. The cultures of paratyphoid C isolated in China by these observers were found to be avirulent for rabbits on subcutaneous injection.

The virulence of the 7 strains of salmonella suipestifer isolated from the cases described above, was studied.

Since rabbits that are carriers of B. enteritidis or B. aertryke, are known to be protected against B. suipestifer, the sera of the rabbits used in these experiments were tested for agglutinins for these organisms before injection. 0.1 cc. of a 1 to 100 dilution of 18-hour broth cultures was injected subcutaneously into rabbits weighing approximately 5 lbs. All, except culture E (case 3), of the monophasic

TABLE 5

Serum no. 270 immunized with the monophasic culture E (Case 3)

CULTURE	ABSORBED WITH												CONTROL		
	Homologous culture E			Monophasic culture J			Specific type of I			Non-specific type of I					
	500	1,000	2,000	500	1,000	2,000	500	1,000	2,000	500	1,000	2,000	500	1,000	2,000
E	−	−	−	−	−	−	3+	3+	3+	−	−	−	4+	4+	4+
G	−	−	−	−	−	−	3+	3+	3+	−	−	−	4+	3+	3+
H	−	−	−	−	−	−	3+	3+	3+	−	−	−	3+	3+	3+
J	−	−	−	−	−	−	3+	3+	3+	−	−	−	4+	4+	2+
K	−	−	−	−	−	−	3+	3+	3+	−	−	−	4+	4+	4+
L	−	−	−	−	−	−	4+	4+	4+	−	−	−	4+	3+	3+
I*	−	−	−	−	−	−	4+	4+	4+	−	−	−	4+	4+	4+

* Non-specific.

group II cultures killed the rabbits in from 8 to 13 days. The E culture failed to kill both on subcutaneous and intravenous injection, and was found, on repeated tests, to be avirulent. The diphasic culture I (case 4) killed in 8 days following the subcutaneous injection of 0.1 cc. of 1 to 100 dilution of an 18-hour broth culture.

The impression obtained from these experiments is that the virulence of the monophasic Group II strains of human origin is somewhat variable. The one diphasic strain, (culture I, case 4) was virulent on subcutaneous injection.

Agglutination of B. suipestifer by the patients' sera 1 to 5 months after discharge. It will be noted that only two of the patients (cases 2 and 4) agglutinated the homologous organism during their stay in the

hospital. Sera have been obtained from all the patients, anywhere from 1 month to 5 months after discharge. The later bleedings from all except one (case 5) of the patients agglutinated the homologous organism in a dilution of 1 to 160 or above. Four of the cases agglutinated several other strains of suipestifer, both porcine and human, in addition to the homologous strain. The serum from case 4 (diphasic) agglutinated both homologous specific and non-specific types and also the specific and non-specific types of the porcine diphasic culture B almost equally well. This serum, furthermore, agglutinated both human and porcine monophasic cultures as shown in the following protocol.

TABLE 6

Serum Case 4. Bled 5/6/32, five months after discharge

CULTURES	SERUM DILUTIONS				
	40	80	160	320	Control
I, specific, homologous	4+	4+	4+	3+	−
I, non-specific, homologous	3+	3+	2+	−	−
B, specific, porcine	4+	4+	4+	−	−
B, non-specific, porcine	4+	4+	4+	−	−
D, porcine monophasic	2+	3+	2+	−	−
K, human monophasic	4+	4+	3+	−	−

DISCUSSION

In the current German literature (13, 14), there has been considerable discussion as to whether the members of animal paratyphoid group to which B. suipestifer belongs are truly pathogenic for man. It seems obvious that these strains isolated from animals are less virulent than typhoid, paratyphoid A and B since the number of infections is so small. The evidence, however, is growing that under certain circumstances, either as a result of massive infection such as occurs in food poisoning, or of a lack of resistance on the part of the host, that members of the animal paratyphoid group are able to excite disease in man. Ten Broeck in his review of five cases, one child and four young adults, expresses the view that B. suipestifer was probably a secondary or terminal invader. In the seven cases reviewed above, the clinical impression in four of them in which there were no compli-

cations, was that B. suipestifer was the etiological agent concerned. It can be stated, however, that this organism does not seem to be very virulent for man, since without complications the cases are mild and there is little evidence of localization in the intestine.

The occurrence of seven cases of B. suipestifer infection in children at the same hospital within four months, is unusual. The other reported cases, have been sporadic.

It is of interest that, while we were studying these cases, a culture obtained by lumbar puncture before death from a patient dying of chronic meningitis at the Baltimore City Hospital, Bay View, was sent to us for identification. It proved to be a monophasic suipestifer (Group II). Unfortunately, the patient was comatose on admission and died shortly afterwards. No adequate history could be obtained.

According to Dr. Ten Broeck (15), the relation of B. suipestifer to the virus of hog cholera is a variable one. When hog cholera was first studied by Theobald Smith, the virus was almost invariably associated with B. suipestifer. From 1910 to 1920 B. suipestifer was only rarely found in cases of hog cholera in the Middle Atlantic States, but in the last three years its prevalence has again increased. These findings would make it seem likely that the amount of infected pork on the market at any one time was subject to great variations. The simplest explanation of these cases of B. suipestifer infection is the accidental contamination of uncooked foods by the hands of a person who had handled infected pork, as is suggested by Krumwiede *et al.* (4). It seems probable that the infected food was eaten shortly after contamination since there was no evidence of food poisoning. The patients did not live near each other and there was no evidence that the same meat market was patronized by all of them. The fact that the mother of one of the patients gave a history of having had a febrile illness and that her blood was found to agglutinate the organism isolated from her son, would seem to indicate that she had suffered from a similar infection. It may well be that eventually it will be shown that there is some other source of infection besides the pig.

It is of interest that both groups of suipestifer (monophasic and diphasic) were represented in this series of cases. Clinically, there seemed to be no striking difference, except that the single case of Group I infection seemed milder than the others.

The mortality in B. suipestifer infections in adults seems to be considerably higher than in children: in the six sporadic cases reported (5) four of the patients died. In Ten Broeck's series in China, consisting of one child and four adults, two of the adults died. The only fatality due to B. suipestifer in children is the case reported by Rau (9). Our cases were all comparatively mild and of short duration.

SUMMARY

1. Seven cases of infection with bacilli of the hog cholera group (Salmonella suipestifer) in children ranging from seven months to six years are described.

2. The organisms were isolated by blood culture in every instance and fell into two groups, six of the cultures belonging to Group II (monophasic) and one to Group I (diphasic).

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BOOK REVIEWS

Brain and Personality. By PAUL SCHILDER, M.D., Ph.D. Pp. 136. $3.00. (*Nervous and Mental Disease Publishing Co., 1931.*)

In the first part, "Studies in the Psychological Aspects of Cerebral Neuropathology," the author outlines his view concerning brain functions. He covers a wide field (problems of consciousness, tonus, encephalitis, optic agnosia, speech disturbance, posture) illustrating with many personal observations and exploiting remarkable command of the literature. In the second part, "The Relations Between the Personality and Motility of Schizophrenics," he utilizes his opportunity to apply psychoanalytic theories to schizophrenic disturbances and to explain catatonic symptoms by neurological analogy.

O. D.

Practical Psychology and Psychiatry. By C. B. BURR, M.D. 6th edition. 369 Pp. (*F. A. Davis and Co., 1930.*)

The sixth edition of this outline for nurses and physicians gives 100 pages to "The Science of Mind," a short chapter on symbolism, obsessions and sex aberrations; a review of the standard forms of psychoses (155 pages); a chapter of nearly 60 pages on the management of cases of insanity, and 30 pages on prevention. Sound practical experiences and simplicity make the author adhere to well seasoned lines.

A. M.

The Commoner Nervous Diseases. For General Practitioners and Students. By FREDERICK J. NATTRASS, Assistant Phys., Royal Victoria Infirmary, Newcastle-Upon-Tyne. Pp. 211. $4.00. (*Oxford University Press, 1931.*)

The purpose of this little book is made clear in the title. There is a short section devoted to history taking and methods of examination and the rest of the volume is composed of brief chapters dealing with disseminated sclerosis, neurosyphilis, subacute combined degeneration of the cord, poliomyelitis, neuritis, the muscular atrophies, epilepsy, cerebral vascular lesions, intracranial tumor, abscess meningitis, epidemic encephalitis, vertigo, migraine, chorea and the psychoneuroses. The author's knowledge of the subject is sound and his presentation is clear. On the whole, the essentials of each disease are given, although the discussion is necessarily brief. A good deal of emphasis has been laid upon therapy. The author admits that he has given less consideration to the physiology and anatomy of the nervous system than is usually considered necessary in undergraduate teaching and believes that the book will be most valuable to the general practitioner who does not wish to cover the entire field of neurology.

F. R. F.

Medical Psychology. By WILLIAM A. WHITE. (*Nervous and Mental Disease Publishing Co., 1931.*)

This book is an interesting attempt to present a psychology of integration with psychoanalytic conceptions. The personality is taken as a whole and the interrelations between mental and physical factors and environmental influences are pointed out and clarified by presentations of case material and quotations from various biologists. The book is well written and easy to read. The wording and certain definitions will, no doubt, cause contradictions and discussion. Many will doubtless entertain a broader view of integration.

O. D.

Problems and Methods of Research in Protozoölogy. Edited by ROBERT HEGNER AND JUSTIN ANDREWS. 532 Pp. Illust. with 32 figures. [In original contributions by 27 authors.] (*Macmillan Co., New York, 1930.*)

This collection of short original articles should prove of special interest to the student of parasitic protozoa. A wide range of material is covered, from a chapter on the protozoa of termites to an excellent discussion of the application of the statistical method in protozoölogy by Lowell J. Read. The several chapters on malaria and amœbiasis, the compilation of standard methods and reagents and the presentation of serological technique in the study of protozoa give the book an immediate practical value in a number of fields of research as well as in routine laboratory procedure. There is appended an extensive bibliography and a comprehensive list of periodicals and books on protozoa. The editors have undoubtedly succeeded in their intention of providing not only a handy reference book but an analytical presentation of problems for the stimulation and promotion of research in the field of protozoölogy.

C. E.

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